WO 2004/089895 PCT/SI2004/000019

15

CLAIMS

- A process for the preparation of amorphous atorvastatin calcium, which
 comprises preparation of calcium salt of atorvastatin in a mixture of solvents
 consisting of a chlorinated organic solvent, a non-hydroxylic organic solvent,
 and water and at which the source of calcium ions is selected from the group
 consisting of calcium acetate and calcium chloride.
- 2. A process for the preparation of amorphous atorvastatin calcium, which comprises preparation of calcium salt of atorvastatin in a mixture of solvents consisting of a cyclic hydrocarbon solvent, a non-hydroxylic organic solvent, and water and at which the source of calcium ions is selected from the group consisting of calcium acetate and calcium chloride.
- 3. A process for the preparation of amorphous atorvastatin calcium according to claim 1, characterized in that the chlorinated organic solvent is selected from the group consisting of chloroform, trichloroethane, dichloromethane and tetrachloroethane.
- 4. A process for the preparation of amorphous atorvastatin calcium according to claim 3, characterized in that the chlorinated organic solvent is chloroform.
- 5. A process for the preparation of amorphous atorvastatin calcium according to claim 3, characterized in that the chlorinated organic solvent is dichloromethane.
- A process for the preparation of amorphous atorvastatin calcium according to claim 2, characterized in that the cyclic hydrocarbon solvent is selected from the group consisting of cyclohexane, cyclopentane and methyl cyclohexane.
- 7. A process for the preparation of amorphous atorvastatin calcium according to claim 6, characterized in that the cyclic hydrocarbon solvent is cyclohexane.

- 8. A process for the preparation of amorphous atorvastatin calcium according to claim 6, characterized in that the cyclic hydrocarbon solvent is cyclopentane.
- A process for the preparation of amorphous atorvastatin calcium according to claim 6, characterized in that the cyclic hydrocarbon solvent is methyl cyclohexane.
- 10. A process for the preparation of amorphous atorvastatin calcium according to claims 1 and 2, characterized in that the non-hydroxylic organic solvent is tetrahydrofuran.
- 11. A process for the preparation of amorphous atorvastatin calcium which comprises:
- a) preparation of a neutral reaction mixture containing sodium salt of atorvastatin,
- addition of chlorinated organic solvent selected from the group consisting of dichloromethane, trichloroethane, tetrachloroethane and chloroform, or addition of cyclic hydrocarbon solvent selected from the group consisting of cyclohexane, cyclopentane, and methyl cyclohexane,
- c) addition of an equivalent or an excess quantity of calcium ions source selected from the group consisting of calcium acetate and calcium chloride,
- d) isolation of atorvastatin calcium.
- 12. A process for the preparation of amorphous atorvastatin calcium according to claim 11 characterized in that the neutral reaction mixture comprising atorvastatin sodium salt is prepared by a process which comprises:
- a) dissolving a compound of formula I or II

$$\begin{array}{c|c} & R_1 & R_2 \\ \hline & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & &$$

wherein R_1 and R_2 may independently represent hydrogen, alkyl with one to three carbon atoms, phenyl, or R_1 in R_2 are taken together as $(-CH_2)_n$ -, wherein n may be 4 or 5;

 R^3 may represent straight or branched chain alkyl of from one to eight carbon atoms or cycloalkyl of from three to six carbon atoms group -O- R_3 may be substituted by the group with the formula:

$$-N$$
 R_{5}

in a non-hydroxylic organic solvent

- b) preparing sodium salt of atorvastatin in a neutral reaction mixture,
- 13. A process for the preparation of amorphous atorvastatin calcium according to claim 12, characterized in that a non-hydroxylic organic solvent is tetrahydrofuran.
- 14. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the neutral reaction mixture comprising sodium salt of atorvastatin shows a pH between 6.5 and 8.0.
- 15. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the chlorinated organic solvent is selected from the group consisting of chloroform, trichloroethane, dichloromethane, and tetrachloroethane.

- 16. A process for the preparation of amorphous atorvastatin calcium according to claim 15, characterized in that the chlorinated organic solvent is chloroform.
- 17. A process for the preparation of amorphous atorvastatin calcium according to claim 15, characterized in that the chlorinated organic solvent is dichloromethane.
- 18. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the cyclic hydrocarbon solvent is selected from the group consisting of cyclohexane, cyclopentane and methyl cyclohexane.
- 19. A process for the preparation of amorphous atorvastatin calcium according to claim 18, characterized in that the cyclic hydrocarbon solvent is cyclohexane.
- 20. A process for the preparation of amorphous atorvastatin calcium according to claim 18, characterized in that the cyclic hydrocarbon solvent is cyclopentane.
- 21. A process for the preparation of amorphous atorvastatin calcium according to claim 18, characterized in that the cyclic hydrocarbon solvent is methyl cyclohexane.
- 22. A process for the preparation of amorphous atorvastatin calcium according to claims 11, characterized in that the chlorinated organic solvent or cyclic hydrocarbon solvent is added in a onefold to fivefold quantity with respect to the existing volume of the solution.
- 23. A process for the preparation of amorphous atorvastatin calcium according to claims 11, characterized in that simultaneously with an addition of the chlorinated organic solvent or cyclic hydrocarbon solvent also a 0.5fold to a twofold quantity of saturated aqueous solution of sodium chloride with respect to the existing volume of the solution is added.

WO 2004/089895 PCT/SI2004/000019

19

- 24. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the isolation of atorvastatin calcium comprises an addition of solvent in which atorvastatin calcium is poorly soluble.
- 25. A process for the preparation of amorphous atorvastatin calcium according to claim 24, characterized in that the solvent in which atorvastatin calcium is poorly soluble, is ether.
- 26. A process for the preparation of amorphous atorvastatin calcium according to claim 25, characterized in that the solvent in which atorvastatin calcium is poorly soluble, is diisopropylether.
- 27. A process for the preparation of amorphous atorvastatin calcium according to claim 11, characterized in that the isolation of atorvastatin calcium comprises:
- a) adding a solvent in which atorvastatin calcium is well soluble,
- b) concentrating the obtained mixture,
- c) adding a solvent in which atorvastatin calcium is poorly soluble so that it, consequently, separates from the reaction mixture.
- 28. A process for the preparation of amorphous atorvastatin calcium according to claim 27, characterized in that the solvent in which atorvastatin calcium is well soluble is selected from the group consisting of methanol, ethanol and propanol.
- 29. A process for the preparation of amorphous atorvastatin calcium according to claim 28, characterized in that the solvent in which atorvastatin calcium is well soluble is methanol.
- 30. A process for the preparation of amorphous atorvastatin calcium according to claim 27, characterized in that the solvent in which atorvastatin calcium is poorly soluble is ether.

WO 2004/089895 PCT/SI2004/000019

20

- 31. A process for the preparation of amorphous atorvastatin calcium according to claim 30, characterized in that the solvent in which atorvastatin calcium is poorly soluble is diisopropylether.
- 32. Use of amorphous atorvastin calcium, prepared by the process as described in any previous claims from 1 to 31 for the preparation of a medicament for the treatment of diseases selected from the group consisting of dislipidemia, hyperlipidemia, hypercholesterolemia, aterosclerosis, arteriosclerosis, cardiovascular diseases, coronary arterial diseases, coronary heart diseases, disorders of blood circulation, inflammation diseases, bone diseases, disorders of processing beta amyloid precursor protein, such as Alzheimer's disease or Down's syndrome.
- 33. A pharmaceutical form comprising amorphous atorvastatin calcium prepared by the process as described in any previous claims from 1 to 32, and pharmaceutically acceptable ingredients.